REMARKS

Status of the Claims

Claims 1-8, 10, 12, and 14-35 are pending. Claims 8 and 14-27 are withdrawn as directed to a non-elected invention. Claims 1-7, 10, 12, and 28-35 are under examination. Claims 1, 28, 29, and 30 are amended to define a particular aspect of the invention. The amendments are made without prejudice or disclaimer. Support for the amendments is found throughout the specification as-filed, including, *e.g.*, on page 19, lines 8-13 and page 31, lines 16-20. Claim 29 is further amended to correct a grammatical error. Reconsideration in view of the amendments and remarks is respectfully requested.

Maintained Rejection

Issues under 35 U.S.C. § 103(a)

Claims 1-7, 10, 12, 28-30, and 33-35 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizobata *et al.*, *British J. Cancer*, 1996, 74:1598-1604, ("Mizobata"), in view of U.S. Patent No. 5,198,423 to Taguchi *et al.* ("Taguchi"). Applicants respectfully traverse the rejection.

The burden is on the Examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc.*, 550 U.S.__. 82 USPQ2d 1385 (2007), the Court affirmed that this analysis includes the following factual inquires: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art. The Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* state that, having undertaken the factual inquires of *Graham*, a rejection under 35 U.S.C. § 103 may be supported by one or more of the following rationales: (1) combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of a known technique to improve similar devices in the same way; (4)

applying a known technique to a known device ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (5) variations that would have been predictable to one of ordinary skill the art; and (6) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention. 72 Fed. Reg. 57526, at 57529 (October 10, 2007). Each of the above-noted rationales requires predictability in the art and/or a reasonable expectation of success, and the Examiner must consider objective evidence, which rebuts such predictability and reasonable expectation of success. This objective evidence or secondary considerations may include unexpected results and/or failure of others (*e.g.*, evidence teaching away from the currently claimed invention), evidence of commercial success, and long-felt but unsolved needs, as found in the specification as-filed or other source. *Id.* When considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at_, 82 USPQ2d at 1396.

Independent claim 1, as amended, is directed to a method for expanding cytotoxic lymphocytes, which comprises: culturing precursor cells, capable of differentiating to cytotoxic lymphocytes, wherein the precursor cells are selected from the group consisting of peripheral blood mononuclear cells, Natural Killer (NK) cells, umbilical cord blood mononuclear cells, hematopoietic stem cells and blood components containing these cells in the presence of at least one fibronectin fragment together with interleukin-2, wherein the fibronectin fragment is a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 19, wherein said culturing is performed for 2-15 days.

Independent claim 28, as amended, is directed to a method for increasing expression of an interleukin-2 receptor in cytotoxic lymphocytes, which comprises: culturing precursor cells, capable of differentiating to cytotoxic lymphocytes, wherein the precursor cells are selected from the group consisting of peripheral blood mononuclear cells, Natural Killer (NK) cells, umbilical cord blood mononuclear cells, hematopoietic stem cells and blood components containing these cells in the presence of at least one fibronectin fragment together with interleukin-2, thereby

increasing expression of interleukin-2 receptor in the cells, wherein the fibronectin fragment is a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 19, wherein said culturing is performed for 2-15 days.

Independent claim 29, as amended, is directed to a method for increasing the number of CD8-positive cells in cytotoxic lymphocytes, which comprises: culturing precursor cells, capable of differentiating to cytotoxic lymphocytes, wherein the precursor cells are selected from the group consisting of peripheral blood mononuclear cells, Natural Killer (NK) cells, umbilical cord blood mononuclear cells, hematopoietic stem cells and blood components containing these cells in the presence of at least one fibronectin fragment together with interleukin-2, thereby increasing the number of CD8-positive cells in the cultured cells, wherein the fibronectin fragment is a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 19, wherein said culturing is performed for 2-15 days.

Independent claim 30 is directed to a method for improving or maintaining cytotoxic activity in cytotoxic lymphocytes, which comprises: culturing precursor cells, capable of differentiating to cytotoxic lymphocytes, wherein the precursor cells are selected from the group consisting of peripheral blood mononuclear cells, Natural Killer (NK) cells, umbilical cord blood mononuclear cells, hematopoietic stem cells and blood components containing these cells in the presence of at least one fibronectin fragment together with interleukin-2, thereby improving or maintaining cytotoxic activity in the cells, wherein the fibronectin fragment is a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 19, wherein said culturing is performed for 2-15 days.

Mizobata teaches culturing a population of peripheral blood mononuclear cells (PMBCs) with tumor cells to induce cytotoxic T lymphocytes ("CTL's"), followed by stimulating the CTL cell population with IL-2, anti-CD3, and fibronectin, *see, e.g.*, page 1599 of Mizobata.

The Examiner relies on Taguchi to describe a biologically active recombinant fibronectin fragment comprising SEQ ID NO: 12. The Examiner further states that Taguchi teaches that the recombinant fibronectin is less costly to produce and of less likely to be infected with, *e.g.*, bacteria and viruses, than natural fibronectin, *see* Office Action, item 8, page 4.

In contrast to the instant claims, Mizobata teaches that PBMCs, which have already differentiated into cytotoxic T lymphocytes, are contacted with fibronectin. Claims 1, 28, 29, and 30, as amended, specify that the PBMCs are "precursor" cells, *i.e.*, undifferentiated PBMCs. (*See*, *e.g.*, page 31, lines 17-18 in the specification as originally filed, which states that a precursor cell " is in a stage before the cell becomes CTL and fated to differentiate to CTL..."). Accordingly, unlike the instant claims, Mizobata describes inducing differentiation in the PBMC cells before contacting the cells with fibronectin. Furthermore, a skilled artisan would not have reasonably expected from Mizobata that culturing a precursor PBMC with fibronectin and interleukin-2, without first inducing the cells to differentiate to CTLs, could have resulted in an expansion of cytotoxic lymphocytes, cytotoxic lymphocytes having improved cytotoxicity, cytotoxic lymphocytes exhibiting an increase in interleukin-2 receptor expression or cytotoxic lymphocytes exhibiting an increase in the number of CD8-positive cells. *See*, *e.g.*, abstract of Mizobata, which describes that the properties of cytotoxic T lymphocytes, *i.e.* differentiated PBMCs, are enhanced by fibronectin.

Tagouchi does not remedy the deficiencies of Mizobata. As noted above, the Examiner only relies on Tagouchi as teaching recombinant fibronectin.

Based upon the foregoing, Applicants submit that neither Mizobata nor Tagouchi, alone or in combination, fail to teach or suggest all of the elements of the instant claims. In addition, Applicants submit that a skilled artisan could not have reasonably expected from the cited references that enhanced properties of cytotoxic lymphocytes could have been obtained from contacting undifferentiated PBMCs with fibronectin. Accordingly, independent claims 1, 28, 29, and 30 are not obvious over the cited references. Dependent claims 2-7, 10, 12, and 33-35, which incorporate the elements of claim 1, are also not obvious over Mizobata and Tagouchi. Applicants respectfully request that the rejection be reconsidered and withdrawn.

New Objection and Rejection

Claim Objection

Claim 29 is objected to for specifying a method for increasing the number of CD8+ cells "in a cytotoxic lymphocytes." Claim 29 is amended to specify "in cytotoxic lymphocytes." Accordingly, Applicants respectfully request withdrawal of the objection.

Issue under 35 U.S.C. § 103(a)

Claims 31-32 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizobata in view of Taguchi and further in view of Chen *et al.*, *J. Immunol.*, 1994, 153:3630-3638 ("Chen"). Applicants respectfully traverse the rejection.

As noted above, neither Mizobata nor Taguchi alone or in combination teach all of the elements of independent claim 1, *e.g.*, contacting undifferentiated PBMCs with fibronectin. Chen does not remedy the deficiencies of Mizobata and Taguchi. The Examiner relies on Chen merely for teaching the transduction of a foreign gene into cytotoxic lymphocytes. Accordingly, claims 31-32, which incorporate all of the elements of independent claim 1, are not obvious over the cited references. Applicants respectfully request the rejection be reconsidered and withdrawn.

Non-statutory Obviousness-type Double Patenting

Claims 1-7, 10, 12, and 28-35 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly unpatentable over claims 1, 8, 15-16, 30, 32, and 34 of co-pending U.S. Application No. 10/486, 512, in view of Mizobata and Chen or over claims 1-15, and 20-21 of co-pending U.S. Application No. 10/568,745 in view of Mizobata.

The Examiner is respectfully requested to hold the provisional rejections in abeyance until allowable subject matter is identified in the present application, *see* M.P.E.P. § 804(I)(B)(1).

CONCLUSION

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Reg. No. 46,046, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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